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Response surface optimization of high dose pellets by extrusion and spheronization

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Summary

A radial basket-type extruder and a serrated plate spheronizer were used to prepare spherical pellets containing approx. 80% active drug. A response surface experimental design was employed to address the effects of altering microcrystalline cellulose concentration, water concentration, spheronizer speed and spheronizing time on pelletization of this low density drug. Response surfaces were adequately described by quadratic equations which contained significant interaction terms for two of three measured product characteristics. Optimum ingredient concentrations and process conditions were selected from the response surface equations. Product subsequently manufactured under these optimum conditions met expectations. This results in a well-characterized, reproducible process for manufacturing smooth pellets with adequate potency to provide a 500 mg dose in a '0' elongated capsule.

Introduction

The objective of the present study was to obtain high drug loaded pellets, sufficiently densified to fill a 500 mg dose into a '0' elongated capsule and with surfaces acceptably smooth for subsequent controlled release coating. Extrusion/spheronization technology was chosen to accomplish this objective. The main processing steps in extrusion/spheronization are dry blending, wet mixing, extrusion of wet granulations into short cylinders and spheronization of this extrudate, using a spinning, serrated plate (Reynolds, 1970; Conine and Hadley, 1970).

The effects of extrusion/spheronization process and formulation variables on final product characteristics have been studied by various investigators (Woodruff and Nuessle, 1972; Malinowski and Smith, 1974; Malinowski and Smith, 1975; O'Connor et al., 1984; Chein and Nuessle, 1985; O'Connor and Schwartz, 1985; Chariot et al., 1987; Lövgren and Lundberg, 1989). Microcrystalline cellulose (MCC) products have been shown to aid spheronization and it has been reported that MCC products containing sodium carboxymethylcellulose (NaCMC) are especially

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useful in producing high dose pellets (O'Connor et al., 1984; O'Connor and Schwartz, 1985) and granulations (Jalal et al., 1972).

Most of the work reported on extrusion/spheronization processes has been completed using twin screw or ram extruders. A recent study (Fielden et al., 1992a) indicated that pellet quality varies with extruder designs (ram vs cylindrical). This was attributed to different shear rates and shear stresses applied in the extrusion process. In the current study, a radial basket-type extruder was used that differs significantly in design from both ram and twin screw extruders. Like the cylindrical extruders, the basket extruder has a short compression zone resulting in low heat buildup, low product holdup and a short exposure time to high pressure gradients.

Various authors (Rowe and Sadeghnejad, 1987; Fielden et al., 1988, 1992b; Staniforth et al., 1988; Millili and Schwartz, 1990; Bains et al., 1991; Elbers et al., 1992) have discussed the relative importance of water in the extrusion/spheronization process. Water has been described as a granulating aid during wet massing, a lubricant during extrusion and a plasticizer during spheronization. MCC is a major component of many extruded products and is considered a requirement for effective spheronization (Newton, 1990). From this, it is clear that the process of extrusion/spheronization is not independent of formulation components. To completely characterize this product, both process and formulation components were examined as variables in a single study, with the objective to simultaneously optimize both. Statistical experimental designs are well suited for exploring both variable types and their interactions in such a study.

Prior work, based on a Plackett-Burman screening design, was used to isolate critical formulation and process parameters affecting the final product characteristics (Hileman et al., 1993). MCC concentration, water concentration, spheronizer speed and spheronizer residence time are the four most significant continuous variables in this process. Significant discrete variables, also identified in the same study, included Avicel RC-591 and the 1.2 mm extruder screen size, which were selected and not changed in the current study. The prior study revealed no significant effects on final product properties as a result of varying wet massing time or extrusion conditions, even though the extruder controls were varied through the machine limits. All non significant variables were fixed at convenient levels during the current experiments.

Materials and Methods

Microcrystalline cellulose (Avicel RC-591, FMC Corp., Philadelphia, PA) was used as the primary spheronizing aid. The model drug (MDL201,040, Marion Merrell Dow Inc., Kansas City, MO) is zwitterionic (isoelectric point ~ 5.5) and was supplied as a fine powder with a mean particle diameter of 10–15 μm. It is poorly soluble in water and common alcohols and has low bulk density (0.18–0.21 g/cm^3).

Powders were blended and wet mixed in a planetary mixer (Hobart N-50, Hobart Corp., North York, Ontario). The wet granulations were passed through a radial basket extruder (Nica Model E-140, Aeromatic Inc., Columbia, MD) and immediately processed in a spheronizer (Nica Model S-320, Aeromatic Inc., Columbia, MD). Pellets were dried in a fluidized bed dryer (Glatt GPCG-1, Glatt Air Techniques Inc., Ramsey, NJ).

Particle size analysis was conducted on a sieve shaker (Ro-Tap Model B, Tyler Industrial Products, Mentor, OH) for 30 min using U.S. standard sieves. Pellet shape was evaluated using a Quantimet 520 image analysis system (Cambridge Instruments Ltd, U.K.).

Experimental Design

A 27-run Box-Behnken design (Table 1), which is a reduced modification of the three-level factorial, consisting of four variables at three levels, was established using PC-based software (Statgraphics, STSC, Inc., Rockville, MD). Response surface designs provide empirical mathematical models describing the effects of continuous process and formulation variables on final product characteristics. The models generated contain

TABLE 1

Box-Behnken design (randomized)

Run order	Avicel concentration (%)	Water concentration [a]	Spheronizer rotational speed (rpm)	Spheronizer residence time (min)
1	21.5	8.6	900	10
2	25.0	8.6	800	10
3	25.0	8.6	1000	10
4	21.5	8.0	1000	10
5	18.0	8.6	900	15
6	18.0	8.6	1000	10
7	21.5	9.2	1000	10
8	21.5	8.0	900	15
9	18.0	8.6	800	10
10	18.0	9.2	900	10
11	21.5	8.6	1000	5
12	25.0	8.6	900	15
13	25.0	8.6	900	5
14	21.5	8.6	900	10
15	21.5	8.0	800	10
16	21.5	9.2	900	5
17	25.0	8.0	900	10
18	18.0	8.0	900	10
19	21.5	9.2	800	10
20	25.0	9.2	900	10
21	21.5	9.2	900	15
22	21.5	8.0	900	5
23	21.5	8.6	800	15
24	18.0	8.6	900	5
25	21.5	8.6	800	5
26	21.5	8.6	1000	15
27	21.5	8.6	900	10

[a] Water concentration is expressed as g of water per formulation percent of Avicel. For example, when Avicel appears at 25% in the formulation, 215 g (8.6×25) of water is added at the '–' design level. At an 18% Avicel concentration, 155 g (8.6×18) of water is added at the same '–' design level. This allows the variation of both the water and Avicel concentrations within workable windows.

quadratic terms and can explain nonlinear responses. This Box-Behnken design also resolves two-factor interaction effects from the primary effects of individual variables.

Water concentration cannot be varied completely independently of MCC concentration without risk of severe over/under wetting of the batch. Therefore, water concentration was varied as a fraction of the MCC concentration in the design. The batch size of each formulation was 0.5 kg. The model drug and Avicel RC-591 were blended in a planetary mixer. Deionized water was added to the mixture to produce wet granulations. After adding water each batch was mixed an additional 5 min, then immediately extruded. Extrusion conditions were not varied, based on the results of the screening experiment (Hileman et al., 1993) and were as follows: feeder speed, 79 rpm; extruder speed, 30 rpm; and extruder screen, 1.2 mm. The resulting extrudate was immediately spheronized. After spheronization, pellets were dried in a fluid bed dryer at 45°C for 15 min. The order of batch manufacture was randomized.

Pellet evaluation

Particle size analysis was conducted using U.S. standard sieves. The 14/20 mesh fraction was

TABLE 2

Results from the Box-Behnken Study

Run order	14–20 mesh sieve fraction (%)	Capsule fill weight (mg) [a]	Mean roundness score
1	91.5	528.8	1.166
2	85.5	482.0	1.183
3	82.5	485.3	1.162
4	87.0	524.9	1.177
5	80.0	549.7	1.186
6	70.5	549.7	1.184
7	85.0	510.8	1.167
8	84.5	521.0	1.170
9	73.5	545.8	1.199
10	90.5	546.9	1.193
11	84.5	515.7	1.185
12	82.5	482.8	1.163
13	88.5	489.8	1.185
14	89.0	527.5	1.180
15	88.0	526.5	1.204
16	89.0	512.3	1.193
17	88.5	501.0	1.180
18	76.5	555.4	1.187
19	89.0	512.6	1.181
20	78.0	481.5	1.170
21	84.5	518.6	1.168
22	81.0	520.2	1.190
23	89.0	518.1	1.170
24	71.0	533.5	1.186
25	91.0	513.7	1.205
26	85.0	527.3	1.158
27	88.5	527.5	1.161

[a] Expressed as mg drug.

chosen as the usable product. Average pellet shape of this 14/20 mesh fraction was characterized using a Quantimet 520 image analysis system which is based on transfer of a two-dimensional image of a representative pellet sample to a video screen and computation of a roundness parameter as follows:

$$\text{Roundness parameter} = \frac{P^2}{4\pi A}$$

where P is the image perimeter, and A denotes the area of a circle having a diameter equal to the average diameter calculated from the image.

A perfect sphere produces a roundness score of 1.00. Pellets with roundness scores of 1.20 or greater have observable defects or distortions. Pellets with roundness scores less than 1.20 appear increasingly more smooth.

Capsule fill weights were determined by hand filling 14/20 mesh pellets into '0' elongated capsules and calculating the amount of drug using its theoretical fraction for each formulation.

Results and Discussion

Bains et al. (1991) reported that the amount of moisture required for successful pellet production is very critical at high drug loads when using microcrystalline cellulose (Avicel PH-101) as a manufacturing aid. Other reports (O'Connor et al., 1984; O'Connor and Schwartz, 1985) have suggested that MCC containing small amounts of NaCMC (Avicel RC-581 and RC-591) is especially useful in pellet formation at high drug loading. This was confirmed in preliminary experiments with the current extrusion/spheronization process (unpublished data). It was observed that the range of water content required for successful pellet production at high drug loading was more narrow with Avicel PH-101 than with Avicel RC

TABLE 3

ANOVA for capsule fill weight response

Effect	Sum of squares	DF	Mean Sq.	*F* ratio	*P* value
A: AVconc [a]	10713.1752	1	10713.175	668.39	0.0000
B: water [b]	364.8724	1	364.872	22.76	0.0005
C: rotate [c]	17.8852	1	17.885	1.12	0.3116
D: reside [d]	86.1352	1	86.135	5.37	0.0389
AB [e]	30.4152	1	30.415	1.90	0.1935
AC	0.0240	1	0.024	0.00	0.9702
AD	133.7492	1	133.749	8.34	0.0136
BC	0.0169	1	0.017	0.00	0.9750
BD	7.5625	1	7.563	0.47	0.5124
CD	12.4609	1	12.461	0.78	0.4045
AA [f]	210.9526	1	210.953	13.16	0.0035
BB	39.0722	1	39.072	2.44	0.1444
CC	142.7840	1	142.784	8.91	0.0114
DD	214.9969	1	214.997	13.41	0.0033
Total error	192.3414	12	16.028		
Total (corr.)	11908.9652	26			
$R^2 = 0.983849$			$R^2 = 0.965006$ (adjusted for degrees of freedom)		

[a] AVconc, Avicel concentration.
[b] Water, water concentration.
[c] Rotate, spheronizer rotational speed.
[d] Reside, spheronizer residence time.
[e] *AB*, interaction term between factor *A*, here AVconc, and factor *B*, here water.
[f] *AA*, quadratic term for factor *A*, here AVconc.

TABLE 4

Significant results summary from the Box-Behnken study (ANOVA)

Variable	Fill weight	Shape	Particle size
Avicel concentration	+ + +0	+ + +	+ + +0
Water concentration	+	+ +	0
Rotational speed	+ +	+ + +	−
Residence time	+ + +0	+	−

+, linear term significant; + +, quadratic term significant; + + +, linear and quadratic terms significant; −, not significant; 0, interaction term(s) significant.

products. The presence of NaCMC enhances the water sorbing capacity (Blair et al., 1990) and thus enhances the water modulating capability of microcrystalline cellulose, in addition to increasing its binding capacity. The results of the screening study (Hileman et al., 1993) confirmed that the RC-591 grade consistently produced more acceptable pellets.

Results of the Box-Behnken study are listed in Table 2. For each experiment, beads were hand-filled into a size '0' elongated gelatin capsule. For purposes of comparison between formulations of different drug concentrations, the fill weight was multiplied by the formulation percentage of drug to yield a theoretical net dose in milligrams per capsule. This is reported as capsule fill weight. Particle size is reported as the fraction of the batch passing a 14 mesh and retained by a 20 mesh U.S. standard sieve. The mean roundness was determined from Quantimet scanning of approx. 250–400 beads, also of the 14/20 mesh fraction.

The ANOVA table for fill weight is presented in Table 3. Both linear and quadratic terms are significant, as well as several interaction terms.

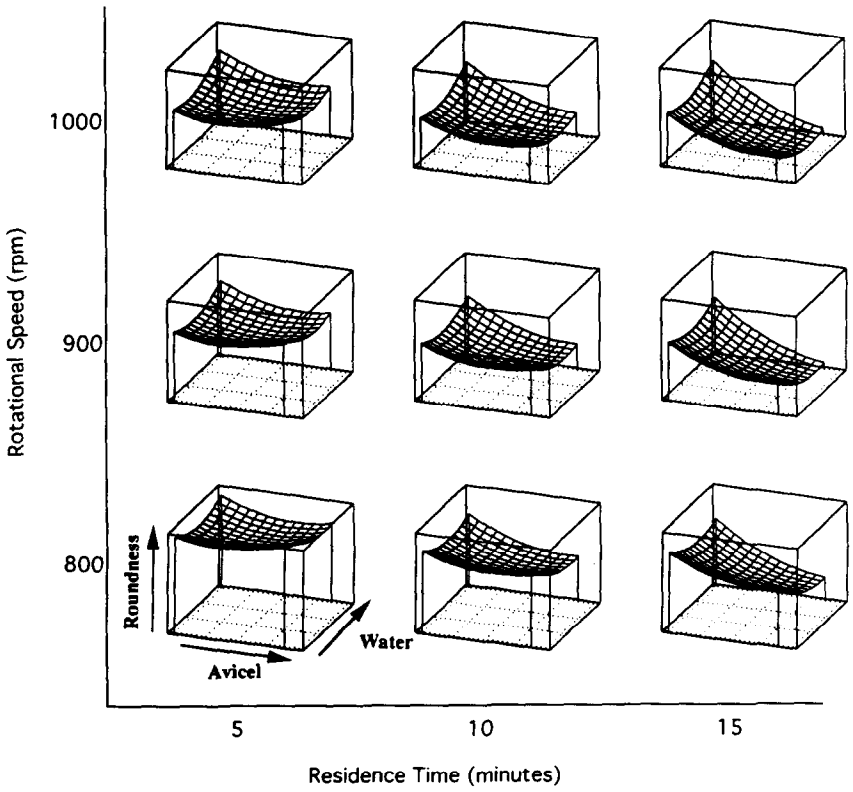

Fig. 1. Estimated response surface plots for mean roundness. Avicel RC-591 (18–25%); water ratio (8.0–9.2); mean roundness (1.10–1.22).

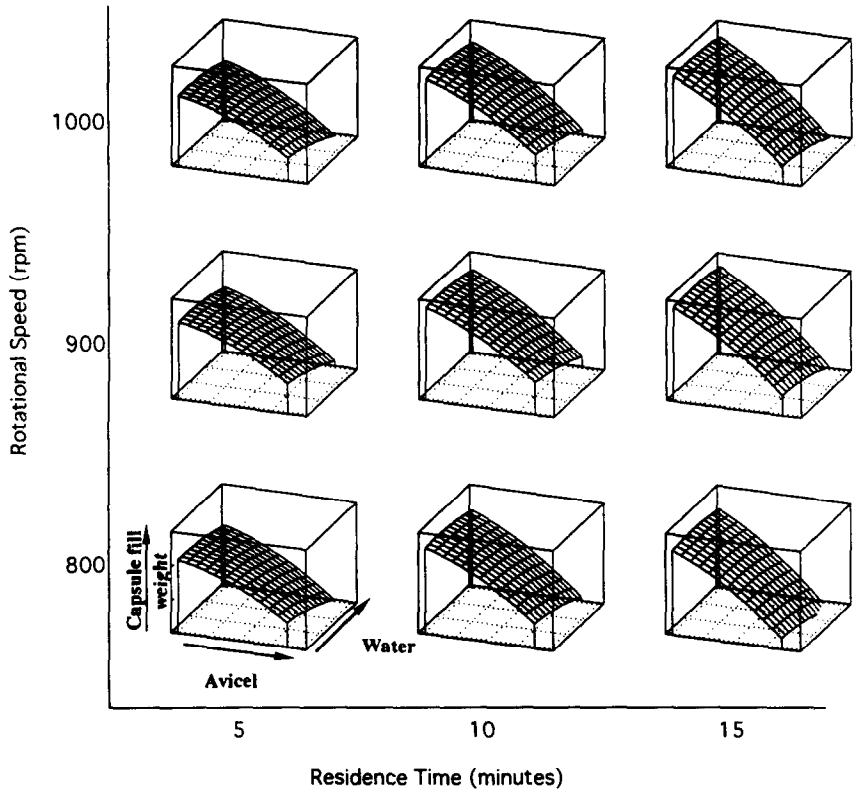

Fig. 2. Estimated response surface plots for capsule fill weights. Avicel RC-591 (18–25%); water ratio (8.0–9.2); capsule fill weights (470–560 mg).

ANOVA yielded similar results for the other two responses, although different variables were significant in those cases. All variables studied had significant effects on one or more responses as summarized in Table 4.

A backward stepwise regression (SAS Institute) was used to generate the following response surface equations. Interaction terms are designated as the product of two factors (e.g., AT = Avicel concentration × residence time).

$$\text{Fill weight} = 82.66 + 13.90A + 0.7928S + 12.05T - 0.3304AT - 0.4450A^2 - 0.5381W^2 - 4.337 \times 10^{-4}S^2 - 0.2205T^2 \quad (r^2 = 0.81)$$

$$\text{Roundness} = 2.794 - 0.2442W - 1.058 \times 10^{-3}S - 2.208 \times 10^{-3}AT + 4.471 \times 10^{-4}A^2 + 1.667 \times 10^{-2}W^2 + 5.4 \times 10^{-7}S^2 + 1.525 \times 10^{-4}T^2 \quad (r^2 = 0.88)$$

$$\text{Particle size} = -770.0 + 51.06A + 64.17W + 4.615T - 2.917AW - 0.2143AT - 0.5302A^2 - 1.016 \times 10^{-5}S^2 \quad (r^2 = 0.98)$$

where A is the Avicel concentration, W denotes the water/Avicel ratio, S is the plate rotational

speed of the spheronizer, and T represents the residence time in the spheronizer.

Response surfaces were plotted for each response using the PC-based Statgraphics program (Figs 1–3). Since all four variables are included in the regression equations for each response, three-dimensional plots of Avicel concentration and water concentration vs the response were drawn at each of three levels of spheronizing speed and time. These nine plots were then embedded on axes representing spheronizing speed and spheronizing time. This presentation allows visualization of the changing response surfaces across all four variables.

Fig. 1 illustrates the response surface plots for roundness score. Moving across any row (increasing spheronizing time), the roundness score surface changes in gross appearance. At short spheronizing times, roundness score is relatively independent of Avicel concentrations. However, at long spheronizing times, the roundness score improves (decreases) sharply with increasing Avicel concentration. In all cases, the water concentration has little effect on roundness score.

In the capsule fill weight response (Fig. 2), no significant shape changes in the surface are seen across changing levels of spheronizing speed or time. This indicates that, relative to the effects of changing Avicel concentration, the spheronizing process variables had little effect on capsule fill weight. This supports the ANOVA results, in which both of the formulation variables were strongly significant, while the spheronizing conditions were less so (Table 3).

In the sieve fraction plot (Fig. 3), starting in the lower left-hand corner which represents low spheronizing time, the effect of increasing spheronizing speed can be observed by moving vertically up the first column of graphs. The gross shape of the surface does not change signifi-

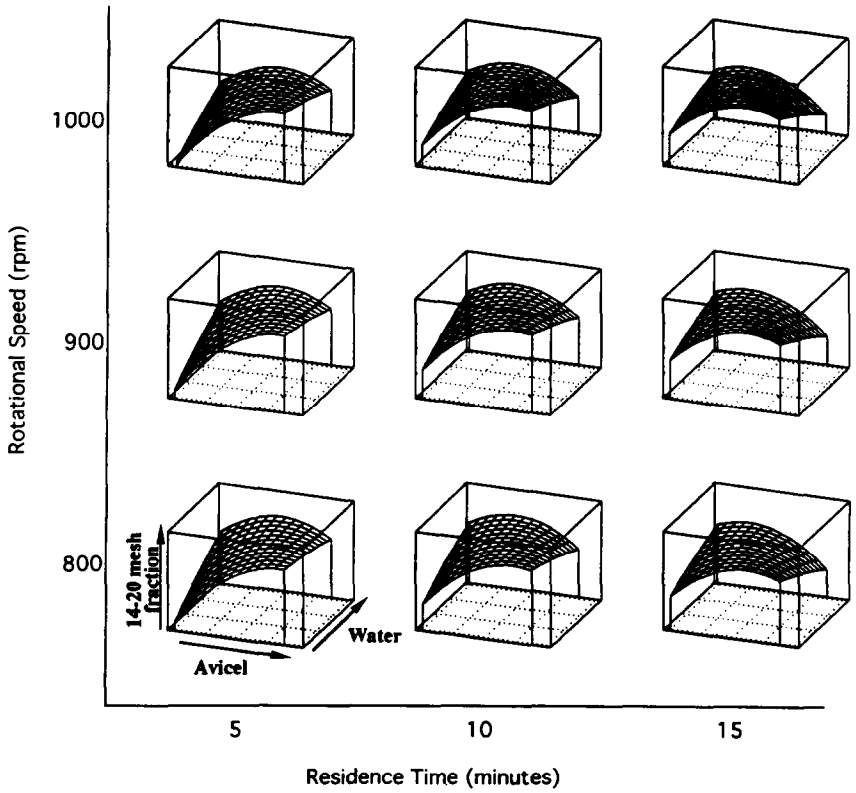

Fig. 3. Estimated response surface plots for 14/20 mesh sieve fractions. Avicel RC-591 (18–25%); water ratio (8.0–9.2); 14/20 mesh sieve fraction (65–100%).

cantly, and the highest yield of 14/20 mesh pellets occurs under conditions of low speed, short time, and maximum Avicel concentration. Moving to the third column, representing the same response at longer spheronizing times, the surface shape changes. In contrast to the optimum conditions at short spheronizing time, the highest yield of acceptable beads now occurs at low Avicel concentration and at the highest water concentration.

Careful study of these plots reveals that the optimum level of each response does not occur at the same variable set points. Thus, a single, optimum condition does not exist for all responses simultaneously. For example, at high concentrations of Avicel, increasing spheronizing times produced more spherical pellets. Under the same conditions capsule fill weight is at a minimum. At low spheronizing times and speeds, high concentrations of Avicel gave higher yields of 14/20 mesh pellets. At high spheronizing times and high spheronizing speeds, medium amounts of Avicel and water gave higher yields in the 14/20 mesh range. An iterative approach to finding a suitable operating range for each variable was undertaken.

A nested 'do loop' was created in SAS to predict results using the response surface models above, at 10 levels of each variable, equally spaced across the experimental range. These calculations resulted in a response matrix containing 10 000 data points representing the four-dimensional response surface of the entire factor space. The data were sorted using the criteria in Table 5. Approx. 200 of these 10 000 data points were identified which met all three sort criteria (minimum acceptable fill weight, high yield of usable fraction and low roundness score). The process and formulation set points from these 200 points were evaluated and found to be normally distributed. The mean set points were calculated to produce a set of optimum operating conditions, providing the best compromised fit to all results (Table 6).

Subsequently, the optimum formulation and process conditions were used to manufacture 20 batches of 500 g each. Average results from these 20 batches are presented in Table 7, along with the values for each predicted from the derived equations. Results compare favorably with predictions.

TABLE 5

Sort criteria for determining the optimum formulation and process conditions

Sort priority	Response	Acceptance level
1	capsule fill weight	≧ 530 mg (pure drug)
2	particle size	≧ 88% (14/20 mesh)
3	mean roundness	≦ 1.175 (score)

TABLE 6

Optimum formulation and operating conditions

Condition	Optimum
Avicel RC-591	20.75%
Water/Avicel ratio	8.7
Spheronizing speed	900 rpm
Spheronizing time	12 min

TABLE 7

Predicted and actual results at optimum operating conditions

Response	20 batch average	Predicted response
Capsule fill weight (mg)	535	531 (526–536)
14/20 mesh (%)	87	86 (84–88)
Mean roundness	1.117	1.081 (1.048–1.119)

Conclusions

Pellets with high drug loads and narrow size distribution were successfully prepared using extrusion/spheronization technology. Approx. 530 mg of the drug could be incorporated into a '0' elongated capsule, providing the required 500 mg dose and allowing for the addition of a controlled release coating at a 5–6% level. Higher drug loads could be successfully achieved using extrusion/spheronization than by traditional layering techniques. The pellets obtained were smooth, spherical and suitable for subsequent coating. A statistical design aided in efficiently characteriz-

ing both formulation and process parameters simultaneously. Mathematical models derived from the designed experimental analysis predicted pellet characteristics very well in subsequent manufacturing trials.

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